

## STATISTICAL ANALYSIS PLAN

**Phase II, randomized, open label, multicenter study in chemotherapy-naïve metastatic Castration-Resistant Prostate Cancer (mCRPC) patients who have primary resistance to Abiraterone acetate or Enzalutamide treatment comparing the anti-tumor effect of Cabazitaxel to alternative Androgen Receptors (AR) targeted therapy**

**XRP6258-LPS14022 / PRIMCAB**

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**Date of issue: 29-Mar-2017**

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Total number of pages: 28

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## LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE:	adverse event
AR:	androgen receptor
ATC:	anatomical therapeutic chemical
BSA:	body surface area
CBZ:	cabazitaxel
CRF:	case report form
CTC:	circulating tumor cell
CTCAE:	common terminology criteria for adverse events
DNA:	deoxyribonucleic acid
ECOG:	Eastern Cooperative Oncology Group
EOT:	end of treatment
HLGT:	high-level group term
HLT:	high-level term
HR:	hazard ratio
IMP:	investigational medicinal product
IVRS/IWRS:	interactive voice/web response system
mCRPC:	metastatic castration-resistant prostate cancer
MedDRA:	Medical Dictionary for Regulatory Activities
PFS:	progression-free survival
PS:	performance status
PSA:	prostate-specific antigen
PT:	preferred term
RECIST:	response evaluation criteria in solid tumors
RNA:	Ribonucleic Acid
rPFS:	radiographic progression-free survival
SAE:	serious adverse event
SOC:	system organ class
SSE:	symptomatic skeletal events
TEAE:	treatment-emergent adverse event
WHO-DD:	World Health Organization-Drug Dictionary

# 1 OVERVIEW AND INVESTIGATIONAL PLAN

## 1.1 STUDY DESIGN AND RANDOMIZATION

This study is a prospective, multicenter, multinational, randomized, stratified, open label, 2-parallel-group.

After a screening phase of up to four weeks, chemotherapy-naïve metastatic castration-resistant prostate cancer (mCRPC) patients, who have primary resistance to Abiraterone acetate or Enzalutamide treatment, will be randomized by an interactive voice/web response system (IVRS/IWRS) in a 1:1 ratio to one of the two treatment groups: cabazitaxel (CBZ) at 25 mg/m<sup>2</sup> plus prednisone (Arm A) versus either Enzalutamide at 160 mg once daily or Abiraterone acetate at 1000 mg once daily plus prednisone (Arm B). The randomization will be stratified by extra nodal visceral metastases (yes/no), level of prostate-specific antigen (PSA) decline within twelve months of initiation of androgen receptor (AR) targeted therapy (no decline, decline 1% to <50%, decline ≥50%) and time from AR targeted agent initiation to progression ([0; 6 months], ]6; 12 months]).

A total of 206 patients (103 patients per arm) from 48 sites (40 in USA and 8 in Canada) will be recruited and randomized to reach the targeted 155 patients with event needed.

The study is event driven and the final cut-off date will be when 155 disease progression events have occurred (expected to occur around 30 months from first patient in).

End of trial will occur 30 days after the last patient last cycle.

A steering committee, including the three study chairmen and sponsor representatives, will be responsible for:

- Supervising the progress of the trial towards its overall objectives,
- Reviewing at regular intervals relevant information that may affect the study conduct,

## 1.2 OBJECTIVES

### 1.2.1 Primary objectives

The primary objective of this study is to demonstrate the superiority of CBZ plus prednisone in comparison with either Abiraterone plus prednisone or Enzalutamide in term of radiographic progression-free survival (rPFS) [using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and Prostate Cancer Working Group criteria 2 (PCWG2)] in chemotherapy-naïve patients with mCRPC who have disease progression while receiving AR targeted therapy (Abiraterone plus prednisone or Enzalutamide) within twelve months of treatment initiation (≤12 months).

### 1.2.2 Secondary objectives

- To compare efficacy of CBZ plus prednisone to Abiraterone acetate plus prednisone or Enzalutamide for:
  - PSA response rate.
  - Progression-free survival (PFS).
  - Overall Survival (OS).
  - Time To PSA Progression (TTPP).
  - Tumor response rate in patients with measurable disease (RECIST 1.1).
  - Duration of tumor response.
  - Pain response.
  - Time to pain progression.
  - Symptomatic skeletal events (SSE) rate.
  - Time to occurrence of any SSE.
- To analyze messenger *Ribonucleic Acid* s (RNAs) including androgen-receptor splice variant 7 messenger RNA (AR-V7) at baseline and post-treatment in Circulating Tumor Cells (CTCs).
- To evaluate safety in the two treatment arms.
- To compare CBZ plus prednisone to Abiraterone acetate plus prednisone or Enzalutamide in term of pain intensity palliation, pain intensity progression, pain intensity interference and pain interference progression.

### 1.2.3 [REDACTED]

- To analyze CTCs phenotypes as well as expression and localization of proteins including AR isoforms in CTCs at baseline.
- To collect circulating free nucleic acids (cfDNA and cfRNA) derived from plasma at baseline, on treatment and post-treatment for biomarker studies.
- To collect germline *deoxyribonucleic acid* (DNA) derived from whole blood at baseline for biomarker studies and subtractive mutation analysis.

### 1.3

Based on bibliographic references cited in the protocol, a hazard ratio (HR) of 0.67 is targeted as the smallest effect of clinical interest. The following table presents how such a HR translates for a variety of envisaged median rPFS in the Abiraterone acetate or Enzalutamide group.

Hazard ratio	Median rPFS (month)	
	Abiraterone acetate or Enzalutamide group	Cabazitaxel group
0.67	4	6.0
0.67	5	7.5
0.67	6	9.0

A total of 155 patients with event is needed to achieve 80% power to demonstrate rPFS superiority of CBZ over Abiraterone acetate or Enzalutamide by one-sided log rank test at 0.05 type I error rate. Further, assuming the accrual is at a constant rate of 4 patients per month for 5 months and then 11 patients per month, a total of 206 patients in two arms (103 patients per arm) is anticipated to be needed to reach the targeted number of patients with event.

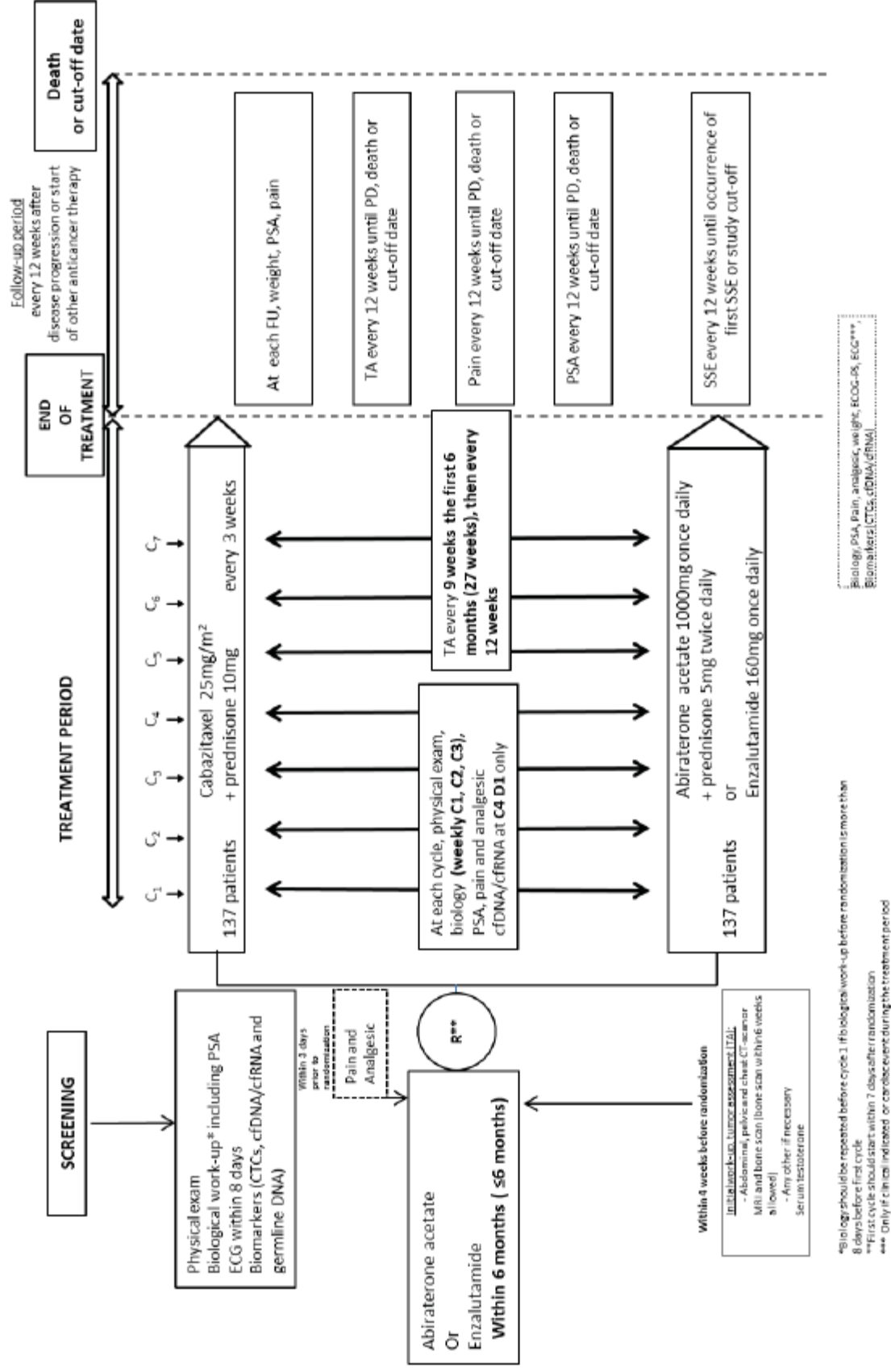
### 1.4 STUDY PLAN

This study comprises three periods:

- Screening period: up to four weeks before randomization.
- Treatment period: it begins at the first study treatment administration within seven days after randomization and ends 30 days after the last treatment administration. Each patient will be treated until radiographic disease progression, unacceptable toxicity or patient's refusal of further study treatment with 3-week cycles. CBZ will be administered intravenously every three weeks. The comparators will be given orally continuously.
- Follow-up period: after study treatment's discontinuation, patient will be followed every 12 weeks until death, cut-off date or withdrawal of patient's consent, whichever comes first. During the follow-up period, all (serious or non-serious) new adverse events (AEs) related to study treatment will be collected and followed until resolution or stabilization. Patients still on study treatment at the cut-off date can continue treatment until reason for study treatment discontinuation planned in the protocol.

For each patient, after the screening visit, a visit per cycle is scheduled with three assessments (Day 01, Day 08 and Day 15) for hematology and biochemistry data collection during the three first cycles, an end of treatment (EOT) visit and a follow-up visit every 12 weeks until death, study cut-off date or withdrawal of patients' consent.





## 1.5

The statistical section of the protocol was changed in amendment 1 dated on 22 February 2016.

### STATISTICAL CONSIDERATIONS-Sample size determination

The following text:

A total of 197 patients with event is needed to achieve 80% power to demonstrate rPFS superiority of Cabazitaxel over abiraterone acetate/prednisone or enzalutamide by 2 sided log rank test at 0.05 type I error rate. Further assuming the accrual is at a constant rate of 15 patients per month, a total of 274 patients in 2 arms (137 patients per arm) are anticipated to be needed to reach the targeted number of patients with event.

Is replaced with:

A total of ~~197~~ 155 patients with event is needed to achieve 80% power to demonstrate rPFS superiority of Cabazitaxel over abiraterone acetate/prednisone or enzalutamide by ~~2~~ one-sided log rank test at 0.05 type I error rate. Further assuming the accrual is at a constant rate of 15 patients per month, a total of ~~274~~ 206 patients in 2 arms (~~137~~ 103 patients per arm) are anticipated to be needed to reach the targeted number of patients with event.

### STATISTICAL CONSIDERATIONS-Primary analysis:

The following text:

Primary analysis will consist of rPFS comparison between abiraterone acetate or enzalutamide group and Cabazitaxel group through a 2-sided 5% log-rank adjusted for the stratification factors (extra nodal visceral metastases, and level of PSA decline) as specified at the time of randomization.

Is replaced with:

Primary analysis will consist of rPFS comparison between abiraterone acetate or enzalutamide group and Cabazitaxel group through a ~~2~~ one-sided 5% log-rank adjusted for the stratification factors (extra nodal visceral metastases, time from AR targeted agent initiation to progression and level of PSA decline) as specified at the time of randomization.

The following text:

The estimates of the hazard ratio and corresponding 95% confidence interval will also be provided using Cox model adjusted for the stratification factors.

Is replaced with:

The estimates of the hazard ratio and corresponding ~~90% and~~ 95% confidence intervals will also be provided using Cox model adjusted for the stratification factors.

## **STATISTICAL CONSIDERATIONS-Interim Analysis:**

The following text deleted:

### **Interim Analysis:**

An interim analysis is planned when approximately 100 rPFS events will have occurred. The purpose of this interim analysis is to provide early stage data to support the planning of potential further clinical trials. The aim of this interim analysis is not to stop the study prematurely as the recruitment is planned to be completed approximately when the interim analysis will take place. Therefore no penalty will be applied to type-I and type-II errors.

## **1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN**

It was decided to discontinue the study due to the very low recruitment rate in both US and Canada involved countries. Only 8 patients were randomized from July 2015 to May 2016 despite a total of 22 sites were initiated.

Therefore, summary tables and/or listing on patient disposition, baseline and demographics data, prior medication, medical history, concomitant medication, exposure, end of treatment/study, deaths of any randomized patient, laboratory data, vital signs and ECG; AE will be provided as well as tables on disposition, overview of AE and description of AE by SOC, HLGT, HLT and PT.

## 2 STATISTICAL AND ANALYTICAL PROCEDURES

### 2.1 ANALYSIS ENDPOINTS

#### 2.1.1 Demographic and baseline characteristics

The baseline value is defined as the last available value before randomization.

##### *Demographic characteristics*

Demographic variables are:

- Age in years (quantitative)
- Race (Caucasian/white, Black, Asian/Oriental, American Indian or Alaska Native, Native Hawaiian or other Pacific Island, other)
- Ethnicity (Hispanic, non-Hispanic).

##### *Medical or surgical history*

Medical or surgical history includes significant prior and concurrent illnesses other than primary prostate tumor cancer surgery.

This information will be coded using the last version available at the time of database lock of Medical Dictionary for Regulatory Activities (MedDRA).

##### *Disease characteristics at baseline*

Not applicable

##### *Prior anti-cancer therapies*

Not applicable

Any technical details related to computation, dates and imputation for missing dates are described in [Section 2.5](#).

#### 2.1.2 Prior or concomitant medications (other than anticancer therapies)

All medications taken within 28 days before randomization or at any time during the study and up to 30 days after the end of study treatment are to be reported in the case report form (CRF) pages.

All medications will be coded using the last version available at the time of database lock of World Health Organization-Drug Dictionary (WHO-DD):

- Prior medications are those the patient used prior to first investigational medicinal product (IMP) administration. Prior medications can be discontinued before first administration or can be ongoing during treatment period.

- Concomitant medications are any treatments received by the patient concomitantly to the IMP from randomization to the end of treatment + 30 days. A given medication can be classified both as a prior medication and as a concomitant medication. Concomitant medications do not include medications started during the post-treatment period (as defined in the observation period in [Section 2.1.4](#)).
- Post-treatment medications are those the patient took in the period running from the day after last IMP administration up to the end of the study.

Any technical details related to computation, dates or imputation for missing dates are described in [Section 2.5](#).

### 2.1.3 Efficacy endpoints

Not applicable

#### 2.1.3.1 Primary efficacy endpoint(s)

Not applicable

#### 2.1.3.2 Secondary efficacy endpoint(s)

Not applicable

### 2.1.4 Safety endpoints

The safety analysis will be based on the reported AEs.

#### *Observation period*

The observation period will be divided into three epochs:

- The **screening** epoch is defined as the time from the signed informed consent date up to first administration of the IMP.
- The **treatment-emergent adverse event** epoch is defined as the time from the date of first administration of the IMP to the date of last administration of the IMP + 30 days.
- The **post-treatment** epoch is defined as the period of time starting the day after the end of the treatment-emergent adverse event period up to the end of the study (defined as last protocol-planned visit or the resolution/stabilization of all serious adverse events (SAEs)).

The on-study observation period is defined as the time from the first study treatment administration until the end of the study (defined as last protocol-planned visit or the resolution/stabilization of all SAEs).

#### **2.1.4.1 Adverse events variables**

##### ***Adverse event observation period***

- Pretreatment adverse events are any AE reported from the signed informed consent date up to the day before the first administration of IMP
- Treatment-emergent adverse events (TEAEs) are AEs reported during the treatment-emergent adverse event period
- Post-treatment adverse events are AEs reported during the post-treatment period

All AEs (including SAEs) will be coded to a lower-level term (LLT), preferred term (PT), high-level term (HLT), high-level group term (HLGT) and associated primary system organ class (SOC) using the last available at the time of database lock of Medical Dictionary for Regulatory Activities (MedDRA).

Record the occurrence of AEs from the time of signed informed consent until the end of the study.

#### **2.1.4.2 Deaths**

The deaths observation period are per the observation periods defined above.

- Death on-study: deaths occurring during the on-study observation period.
- Death on-treatment: deaths occurring during the treatment-emergent adverse event period.
- Death post-study: deaths occurring after the end of the study.

#### **2.1.4.3 Laboratory safety variables**

Clinical laboratory data consists of blood analysis, including hematology, clinical chemistry and dipstick urinalysis. Clinical laboratory values after conversion will be analyzed into standard international units and international units will be used in all listings and tables.

Blood samples for clinical laboratories will be taken within eight days prior Day1 cycle 1, weekly (D8 and D15) during the first three cycles (+/- 1 day window is allowed for hematology) and before each study treatment administration (-3 days window is allowed) for the other cycles.

Creatinine clearance (CrCl) should be evaluated at baseline and before each treatment cycle in case of creatinine increase  $>1 \times$  upper limit of normal (ULN).

Urine dipstick will be performed at baseline and in case of serum creatinine increase by 1.5 fold above baseline or CrCl  $<50$  mL/min.

The laboratory parameters will be classified as follows:

- Hematology
  - **Red blood cells (RBC) and platelets and coagulation:** hemoglobin (g/L), platelet count ( $10^9/L$ ), international normalized ratio (INR).
  - **White blood cells (WBC):** WBC count ( $10^9/L$ ), neutrophils ( $10^9/L$ ), lymphocytes ( $10^9/L$ ), monocytes ( $10^9/L$ ), basophils ( $10^9/L$ ), eosinophils ( $10^9/L$ ).

- Clinical chemistry
  - **Metabolism:** glucose (mmol/L), total protein (g/L), albumin (g/L).
  - **Electrolytes:** sodium (mmol/L), potassium (mmol/L), calcium (mmol/L), phosphorus (mmol/L), magnesium (mmol/L).
  - **Renal function:** creatinine (μmol/L), CrCl (mL/min), blood urea nitrogen (BUN) (mmol/L).
  - **Liver function:** alanine aminotransferase (ALT) (IU/L), aspartate aminotransferase (AST) (IU/L), alkaline phosphatase (IU/L), lactate dehydrogenase (LDH) (IU/L), total bilirubin (μmol/L).
- Endocrinological: testosterone (ng/mL) at baseline.
- Dipstick urinalysis:
  - **Abnormal results** (yes/no), if yes:
  - **WBC** (yes/no)
  - **RBC** (yes/no)
  - **Proteins** (yes/no)
  - **Glucose** (yes/no)

Technical formulas are described in [Section 2.5.1](#).

#### **2.1.4.4 Vital signs variables**

Vital signs include: heart rate (bpm), systolic and diastolic blood pressure (mmHg), weight (kg), body surface area (BSA) (m<sup>2</sup>) and Eastern Cooperative Oncology Group (ECOG), performance status (PS) when post-baseline assessments are available.

#### **2.1.4.5 Electrocardiogram variables**

ECGs will be recorded automatically by the device at the investigator site. ECG results (normal, abnormal and if abnormal clinically significant or not) will be collected within eight days before randomization and at the EOT visit only if clinically indicated or cardiac event during the treatment period.

#### **2.1.4.6 Other safety endpoints**

Not applicable.

#### **2.1.5 Pharmacokinetic variables**

Not Applicable.

#### **2.1.6 Pharmacodynamic/genomics endpoints**

Not Applicable.

### **2.1.7 Quality-of-life endpoints**

Not Applicable.

### **2.1.8 Health economic endpoints**

Not Applicable.

### **2.1.9 Further therapy after discontinuation of investigational medicinal product administration during the study**

Not applicable.

## **2.2 DISPOSITION OF PATIENTS**

This section describes patient disposition for both patient study status and the patient analysis populations.

Screened patients are defined as patients with a date of screening visit and a signed informed consent.

Randomized patients consist of all patients with a signed informed consent form who have had a treatment kit number allocated and recorded in the IVRS/IWRS database, regardless of whether the treatment kit was used.

For patient study status, a listing provided the total number of patients in each of the following categories will be presented in the clinical study report using a summary table:

- Screened patients.
- Screen failures
- Non-randomized but treated patients.
- Randomized patients.

For randomized patients, a listing will displayed information below:

- Treatment group
- Stratification factors:
  - Extra nodal visceral metastases (yes/no),
  - PSA decline within 12 months of initiation of AR targeted therapy (no decline, decline 1% to <50%, decline  $\geq$ 50%),
  - Time from AR targeted agent initiation to progression ([0; 6 months], [6; 12 months]).
- Randomized and treated patients (Safety population).
- Patients who discontinued study treatment by main reason for permanent treatment discontinuation.
- Status at last study contact (given in the patient vital status CRF page).



For all categories of patients (except for the screened and nonrandomized categories) percentages will be calculated using the number of randomized patients as the denominator. Reasons for treatment discontinuation will be supplied with a listing.

### **2.2.1 Randomization and drug dispensing irregularities**

Not applicable.

## **2.3 ANALYSIS POPULATIONS**

Patients treated without being randomized will not be considered randomized.

Patients allocated outside the IVRS/IWRS will not be taken into account in any of the analyses.

The randomized population includes any patient who has been allocated to a randomized treatment regardless of whether the treatment kit was used.

For any patient randomized more than once, only the data associated with the first randomization will be used.

### **2.3.1 Efficacy populations**

Not applicable.

#### **2.3.1.1 *Intent-to-treat population***

Not applicable.

### **2.3.2 Safety population**

This population includes all randomized patients who receive at least one dose (either full or partial dose) of the study drug. This population is for all safety analyses. All analyses using this population will be based on the treatment actually received (ie, “as treated”).

In addition:

- Non randomized but treated patients will not be part of the safety population.
- Randomized patients for whom it is unclear whether they took the IMP will be included in the safety population as randomized.
- For patients receiving more than one study treatment during the trial, as soon as a patient will receive any study drug injection of CBZ, he is considered as a CBZ treated patient.

## 2.4 STATISTICAL METHODS

### 2.4.1 Demographics and baseline characteristics

Listings of parameters described in [Section 2.1.1](#) will be performed on the randomized population sorted by treatment group.

### 2.4.2 Prior or concomitant medications (other than anticancer therapies)

The prior and concomitant medications will be presented for the randomized population.

Medications will be listed by treatment group according to the WHO-DD dictionary, considering the first digit of the Anatomical Therapeutic Chemical (ATC) (anatomic category) and the first three digits of the ATC class (therapeutic category). All ATC codes corresponding to a medication will be summarized and patients will be counted once in each ATC category (anatomic or therapeutic) linked to the medication. Therefore patients may be counted several times for the same medication.

### 2.4.3 Extent of investigational medicinal product exposure and compliance

The extent of IMP exposure and dose information will be listed and sorted by actual treatment within the safety population ([Section 2.3.2](#)).

#### 2.4.3.1 Extent of investigational medicinal product exposure

The extent of exposure will be assessed by the duration of exposure within the safety population.

The number of cycles administered will be presented.

Duration of exposure is defined as last dose date – first dose date + 21 days, regardless of unplanned intermittent discontinuations (see [Section 2.5.3](#) for calculation in case of missing or incomplete data).

#### For CBZ arm:

Dose information will be assessed by the following variables:

- The actual dose received ( $\text{mg}/\text{m}^2$ ) by cycle is defined as (actual dose (mg) collected in the CRF/ BSA ( $\text{m}^2$ )).
- Cumulative dose ( $\text{mg}/\text{m}^2$ ): the cumulative dose for a time period (a given cycle or during the study) is the sum of all “actual” doses received during this time period.
- Overall duration of dosing (weeks) is defined as (last IMP administration – first IMP administration + 21)/7.
- The dose intensity ( $\text{mg}/\text{m}^2/3$  weeks) is defined as the cumulative dose during the study divided by overall duration of dosing multiplied by 3.

- The relative dose intensity (%) is defined as the ratio of the dose intensity to the planned dose intensity. The planned dose intensity (mg/m<sup>2</sup>/3 weeks) is defined as (theoretical dose of 25 mg/m<sup>2</sup> × number of cycles ×3 / overall duration of dosing).
- Dose reduction will be derived by comparing actual dose for a given cycle with the actual dose of the previous cycle.
- Dose delays: a cycle is deemed to have been delayed if start date of the current cycle – start date of previous cycle >21days.

**For comparators arm:**

A cycle is defined as a complete 21 days period.

Dose information will be assessed by the following variables and listed by treatment:

- Total actual dose (mg).
- Cumulative dose (mg) over the treatment period
- Dose reduction

**2.4.4 Analyses of efficacy endpoints**

**2.4.4.1 Analysis of primary efficacy endpoint(s)**

Not applicable.

**2.4.4.2 Analyses of secondary efficacy endpoints**

Not applicable.

**2.4.4.3 Multiplicity issues**

Not applicable.

**2.4.4.4 Additional efficacy analysis(es)**

Not applicable.

**2.4.5 Analyses of safety data**

The safety results will be listed and sorted by treatment group.

***General common rules***

All safety analyses will be performed on the safety population as defined in [Section 2.3.2](#).

### **2.4.5.1 Analyses of adverse events**

#### ***Generalities***

The primary focus of AE reporting will be on TEAEs.

If an AE date/time of onset (occurrence, worsening or becoming serious) is incomplete, an imputation algorithm will be used to classify the AE as pretreatment, treatment-emergent or post-treatment. The algorithm for imputing date/time of onset will be conservative and will classify an AE as treatment emergent unless there is definitive information to determine it is pretreatment or post-treatment. Details on classification of AEs with missing or partial onset dates are provided in [Section 2.5.3](#).

The grade will be taken into account in the summary. For patients with multiple occurrences of the same event, the maximum grade is used.

The table of all TEAEs will present the number (n) and percentage (%) of patients experiencing an AE by SOC (sorted by internationally agreed order), HLGT, HLT and PT (sorted in alphabetical order) for each treatment group.

#### ***Analysis of all treatment-emergent adverse events***

The following TEAE summaries will be generated for the safety population.

- Overview of TEAEs, summarizing number (%) of patients with any
  - TEAE
  - Grade 3-4 TEAE
  - Serious TEAE
  - TEAE leading to death (fatal outcome)
  - TEAE leading to permanent treatment discontinuation.
- All TEAEs by primary SOC, HLGT, HLT and PT, showing number (%) of patients with at least one TEAE, sorted by the SOC internationally agreed order. The other levels (HLGT, HLT and PT) will be presented in alphabetical order.
- All TEAEs by primary SOC and PT, showing number (%) of patients with at least one TEAE, sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC.
- All non-serious TEAEs by primary SOC, HLGT, HLT and PT, showing number (%) of patients with at least one TEAE with a frequency of at least 5%, sorted by the SOC internationally agreed order. The other levels (HLGT, HLT and PT) will be presented in alphabetical order.
- All non-serious TEAEs by primary SOC and PT, showing the number (%) of patients with at least one TEAE with a frequency of at least 5%, sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC.

***Analysis of all treatment emergent serious adverse event(s)***

- All serious TEAEs by primary SOC, HLGT, HLT and PT, showing the number (%) of patients with at least one serious TEAE, sorted by the internationally agreed SOC order. The other levels (HLGT, HLT and PT) will be presented in alphabetical order.
- All serious TEAEs by primary SOC and PT, showing the number (%) of patients with at least one TEAE, sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC.

***Analysis of all treatment-emergent adverse event(s) leading to treatment discontinuation***

- All TEAEs leading to treatment discontinuation, by primary SOC, HLGT, HLT and PT, showing the number (%) of patients sorted by the internationally agreed SOC order. The other levels (HLGT, HLT and PT) will be presented in alphabetical order.
- All serious TEAEs leading to treatment discontinuation, by primary SOC, HLGT, HLT and PT, showing the number (%) of patients sorted by the internationally agreed SOC order. The other levels (HLGT, HLT and PT) will be presented in alphabetical order.

Listings below will be provided:

- All TEAE
- TEAE leading to permanent treatment discontinuation
- TEAE leading to treatment delayed or reduced
- SAE leading to treatment discontinuation
- Reasons for treatment discontinuation.

**2.4.5.2 Deaths**

Summaries of TEAEs leading to death regardless of relationship and related to IMP, by primary SOC, HLGT, HLT and PT will be provided, showing number (%) of patients sorted by internationally agreed SOC order, with HLGT, HLT and PT presented in alphabetical order within each SOC and in order of worst national cancer institute common terminology criteria for adverse events (NCI CTCAE) grade.

A listing of TEAE and/or SAE leading to death and reasons of death will be generated on the randomized patients

**2.4.5.3 Analyses of laboratory variables**

Hematological and clinical biochemistry toxicities will be assessed from laboratory test parameters. Each test result will be graded by NCI CTCAE (version 4.0).

Listing for hematology, clinical chemistry, endocrinological and dipstick urinalysis variables will be provided by treatment group and by cycle. If any, abnormalities will be presented by grade.

#### **2.4.5.4 Analyses of vital sign variables**

Listings of height, weight, BSA, blood pressure (systolic and diastolic), heart rate and ECOG PS will be provided by treatment group and by cycle.

#### **2.4.5.5 Analyses of electrocardiogram variables**

Interpretation of ECG will be listed at the screening and EOT (if available) visits by treatment group.

#### **2.4.6 Analyses of pharmacokinetic and pharmacodynamic variables**

Not applicable.

#### **2.4.7 Analyses of quality of life/health economics variables**

Not applicable.

### **2.5 DATA HANDLING CONVENTIONS**

#### **2.5.1 General conventions**

##### ***Demographic formulas***

Age (years) = Integer [(Date of screening visit – Date of birth)/365.25]

In case of missing data apply these rules:

- missing Day: assume = 15
- missing Month: assume = 6
- missing Year: calculations cannot be done.

In case of incomplete dates, see [Section 2.5.3](#).

$$BSA (m^2) = 0.007184 \times \text{Height(cm)}^{0.725} \times \text{Weight(kg)}^{0.425}$$
 (the variation of DuBois and DuBois formula)

##### ***Laboratory data***

Conversion of laboratory data from used units to international units will be done, if necessary, using the GMA\_rfactor file containing conversion factors for all parameters mentioned in this SAP.

The NCI CTCAE grade of laboratory data will be calculated using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 and ULN and lower limit of normal (LLN) values given in the file EFC6193\_LABNR\_GENERIC.

[http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE\\_4.03\\_2010-06-14\\_QuickReference\\_5x7.pdf](http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf).

## **2.5.2 Data handling conventions for secondary efficacy variables**

Not applicable.

## **2.5.3 Missing data**

### ***Handling of computation of treatment duration if investigational medicinal product end of treatment date is missing***

For the calculation of the treatment duration, the date of the last dose of IMP is equal to the date of last administration reported on the last cycle performed. If this date is missing, the exposure duration should be left as missing.

The last dose administration should be clearly identified in the CRF and should not be approximated by the last returned package date.

### ***Handling of medication missing/partial dates***

No imputation of medication start/end dates or times will be performed. If a medication date or time is missing or partially missing and it cannot be determined whether it was taken prior or concomitantly, it will be considered a prior, concomitant and post-treatment medication.

### ***Handling of adverse events when date and time of first investigational medicinal product administration is missing***

When the date and time of the first IMP administration is missing, all AEs that occurred on or after the day of randomization should be considered as TEAEs.

### ***Handling of missing dates for times calculations***

Not applicable.

## **2.5.4 Windows for time points**

No time windows will be defined.

## **2.5.5 Unscheduled visits**

Not applicable.

## **2.5.6 Pooling of centers for statistical analyses**

Not applicable.

## **2.5.7 Statistical technical issues**

Not applicable.

### **3 INTERIM ANALYSIS**

Not applicable.



## **4 DATABASE LOCK**

The database is planned to be locked one month after last patient last visit (LPLV).

## **5 SOFTWARE DOCUMENTATION**

All summaries and statistical analyses will be generated using SAS version 9.2.

## **6 REFERENCES**

Not applicable.